



Evaluating prediction strategies for identification of T cell responsive mutation-derived neoepitopes in cancer

Andersen, Malene Rask; Bjerregaard, Anne-Mette; Fugmann, T.; Donia, M.; Bentzen, Amalie Kai; Andersen, R.; Szallasi, Zoltan Imre; Neri, D.; Svane, I. M.; Eklund, A. C.

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surveillance. We monitored by flow cytometry both ex vivo and after in vitro stimulation of PBMCs multiple parameters related to

- (i) levels of Tregs; MDSCs; myeloid and plasmacytoid dendritic cells;
- (ii) the responsiveness of T cells to anti-CD3 and APCs to pro-inflammatory stimuli and
- (iii) the immune-phenotype of naïve and tumor specific memory T cells.

The results show in samples from patients after three cycles of A/C, a T cell responsiveness and maturation of DCs not observed in pre-chemotherapy samples. Interestingly, the T cell responsiveness highly correlate with IL-12 secretion by CD83+ DCs. Using principal component analysis (PCA), our immune-monitoring model shows a significant difference among pre- and post-chemotherapy patients compared with healthy donors that correlates with tumor regression.

The PCA lead us to propose an immune stimulating role attributed to A/C characterized by immune responsiveness of T and APC compartments to different stimuli in post-chemotherapy samples with levels close to those exhibited by healthy donors not observed in the pre-chemotherapy samples.

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Evaluating prediction strategies for identification of T cell responsive mutation-derived neo-epitopes in cancer

Andersen, S.R.¹, Bjerregaard, A.-M.², Fugmann, T.³, Donia, M.⁴, Bentzen, A.K.¹, Andersen, R.⁴, Szallasi, Z.², Neri, D.³, Svane, I.M.⁴, Eklund, A.C.², Hadrup, S.R.¹

¹Technical University of Denmark, Section for Immunology and Vaccinology, Frederiksberg C, Denmark, ²Technical University of Denmark, Center for Biological Sequence Analyses, Lyngby, Denmark, ³Philochem AG, Zürich, Switzerland, ⁴University Hospital Herlev, Center for Cancer Immune Therapy, Herlev, Denmark

Increasing evidences point to an important role of mutation-derived antigens in immune recognition of cancer. Current strategies for prediction of immunogenic neoepitopes results in large personalized peptide libraries, but only a minority (< 1%) elicit T cell responses at detectable levels. Neoepitopes are of potential valuable as predictors of response to therapy and targets for personalized immunotherapeutic approached. Consequently, there is an unmet need to understand the rules identifying immunogenic neoepitopes.

Both tumor mutation mapping via exome sequencing and mass-spectrometry-based elution for MHC class I presented peptides has been applied in different studies, combined with RNA sequencing to determine the expression level of relevant transcripts. Additionally, neoepitopes may be defined based on either autologous tumor cell lines or snapfrozen tumor material. We present here a study in which all the above mentioned strategies are assessed in three melanoma patients. Predicted large peptide libraries matching the HLA expression of the patients was identified and selected based on any of the strategies given above. This resulted in a total of ~3000 peptides for the three patients. We investigated the T cell recognition of these personalized peptide libraries using a new technology based on DNA-barcode labeled MHC multimers to detect multiple, potentially > 1000, different neoepitope specific T cell populations in a single sample. Through this unbiased comparison, we evaluate selection strategies for prediction of immunogenic cancer-associated neoepitopes, and identify rules for precise prediction. Precise prediction is essential for future application of neoepitopes both as predictors of responses to therapy and immunotherapeutic targets.

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Features of cancer associated fibroblasts that resemble circulating fibrocytes which constitute a unique subset of MDSCs

Gunaydin, G., Guc, D.

Hacettepe University Cancer Institute, Department of Basic Oncology, Ankara, Turkey

The role of tumor stroma in the functional insufficiency of tumor-infiltrating T-cells has not yet been well determined. Circulating-fibrocytes represent a novel MDSC subset and they take part in the tumor immune escape. Fibroblasts turn into cancer-associated-fibroblasts(CAFs) in the tumor microenvironment. Our aim is to evaluate if CAFs demonstrate similar molecular/gene expression